



214683.ST25
SEQUENCE LISTING

H. 1

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Long, Ya-Qiu

Lung, Feng-Di T

King, Richter C

Yang, Dajun

<120> REDOX-STABLE, NON-PHOSPHORYLATED CYCLIC PEPTIDE INHIBITORS OF SH2 DOMAIN BINDING TO TARGET PROTEIN, CONJUGATES THEREOF, COMPOSITIONS AND METHODS OF SYNTHESIS AND USE

<130> 214683

<140> 09/998,350

<141> 2001-11-30

<150> PCT/US00/15201

<151> 2000-06-02

<150> 60/137,187

<151> 1999-06-02

<160> 19

<170> PatentIn version 3.1

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<223> Synthetic
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<221> misc_feature
<222> (1)..(1)
<223> xaa = Gla, which is gamma-carboxy-L-glutamic acid

<220>
<221> misc_feature
<222> (9)..(9)
<223> Tyr at position 9 is an amide, i.e. C(O)NH

<220>
<221> misc_feature
<222> (1)..(9)
<223> xaa (Gla) and Tyr at position 9 are bridged together, making this peptide cyclic

<400> 1
xaa Leu Tyr Glu Asn Val Gly Met Tyr
1 5

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<222> (1)..(1)
<223> xaa at position 1 is alpha-amino-adipic acid (Adi)

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<222> (4)..(4)
<223> xaa at position 4 is Glu or Adi

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<222> (9)..(9)
<223> Tyr at position 9 is an amide, i.e., C(O)NH

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<221> misc_feature
<222> (1)..(9)
<223> xaa at position 1 and Tyr at position 9 are bridged together, making this peptide cyclic

<400> 2
Xaa Leu Tyr Xaa Asn Val Gly Met Tyr
1 5

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<213> Artificial Sequence

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<223> Synthetic
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<221> misc_feature
<222> (1)..(1)
<223> xaa is any amino acid other than Glu

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<221> misc_feature

<222> (9)..(9)

<223> Tyr at position 9 is an amide, i.e., C(O)NH

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<222> (1)..(9)

<223> Xaa and Tyr at position 9 are bridged together, making this peptide cyclic

<400> 3

Xaa Leu Tyr Glu Asn Val Gly Met Tyr
1 5

<210> 4

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<222> (1)..(1)

<223> Xaa = Gla, which is gamma-carboxy-L-glutamic acid

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<221> misc_feature

<222> (10)..(10)

<223> Cys at position 10 is an amide, i.e., C(O)NH

<220>

<221> misc_feature

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<222> (1)..(10)

<223> xaa (Gla) and Cys are bridged together, making this peptide cycli
c

<400> 4

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys
1 5 10

<210> 5

<211> 10

<212> PRT

<213> Artificial sequence

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<223> Synthetic

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<222> (1)..(1)

<223> Xaa = Gla, which is gamma-carboxy-L-glutamic acid

<400> 5

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys
1 5 10

<210> 6

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<222> (1)..(1)

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<223> xaa = Gla(OtBu)2, which is di- tert-butoxy-gamma-carboxy-L-glutamic acid

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<222> (3)..(3)

<223> Tyr at position 3 is modified to Tyr(tBu), which is tert-butyl-tyrosine

<220>

<221> misc_feature

<222> (4)..(4)

<223> Glu at position 4 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc_feature

<222> (5)..(5)

<223> Asn at position 5 is modified to Asn(Trt), which is trytyl-asparagine

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<221> misc_feature

<222> (9)..(9)

<223> Tyr at position 9 is modified to Tyr(tBu), which is tert-butyl-tyrosine

<220>

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<222> (10)..(10)

<223> Cys at position 10 is modified to Cys(Trt), which is trytyl-cysteine, and Cys(Trt) is connected to a resin

<400> 6

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Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys
1 5 10

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<221> misc_feature

<222> (1)..(1)

<223> xaa = Gla, which is gamma-carboxy-L-glutamic acid

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<222> (1)..(1)

<223> xaa has a C1CH2C(O)- group attached

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<222> (9)..(9)

<223> Tyr at position 9 has a -C(CH2SH)C(O)NH2 group attached

<400> 7

Xaa Leu Tyr Glu Asn Val Gly Met Tyr
1 5

<210> 8

<211> 10

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<222> (1)..(1)
<223> Xaa = Adi, which is alpha-amino-adipic acid

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<222> (1)..(1)
<223> xaa has a CH₂CO- group attached

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<221> misc_feature
<222> (10)..(10)
<223> Cys is an amide, i.e., C(=O)NH

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<221> misc_feature
<222> (1)..(10)
<223> Xaa (Adi) and Cys are bridged together, making this peptide cyclic

<400> 8
Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys
1 5 10

<210> 9
<211> 10
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<213> Artificial Sequence

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<223> Synthetic

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<221> misc_feature

<222> (1)..(1)

<223> At position 1, Xaa = Adi, which is alpha-amino-adipic acid

<220>

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<222> (4)..(4)

<223> At position 4, Xaa = Adi, which is alpha-amino-adipic acid

<220>

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<222> (10)..(10)

<223> Cys is an amide, i.e., C(=O)NH

<220>

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<222> (1)..(10)

<223> Xaa (Adi) at position 1 and Cys are bridged together, making this peptide cyclic

<400> 9

Xaa Leu Tyr Xaa Asn Val Gly Met Tyr Cys
1 5 10

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<223> Synthetic

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<220>
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<222> (1)..(1)
<223> Glu has a CH₂CO- group attached

<220>
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<222> (8)..(8)
<223> Xaa = Nle, which is norleucine

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<222> (1)..(10)
<223> Glu and Cys are bridged together, making this peptide cyclic

<400> 10
Glu Leu Tyr Glu Asn Val Gly Xaa Tyr Cys
1 5 10

<210> 11
<211> 10
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<220>
<223> Synthetic
<220>
<221> misc_feature
<222> (1)..(1)
<223> Glu at position 1 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220> Page 10

<221> misc_feature

<222> (3)..(3)

<223> Tyr at position 3 is modified to Tyr(OtBu), which is tert-butoxy-tyrosine

<220>

<221> misc_feature

<222> (4)..(4)

<223> Glu at position 4 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc_feature

<222> (5)..(5)

<223> Asn at position 5 is modified to Asn(Trt), which is trityl-asparagine

<220>

<221> misc_feature

<222> (9)..(9)

<223> Tyr at position 9 is modified to Tyr(OtBu), which is tert-butoxy-tyrosine

<220>

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<222> (10)..(10)

<223> xaa = Nle, which is norleucine

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<222> (10)..(10)

<223> xaa is an amide and is attached to a resin

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<400> 11

Glu Leu Tyr Glu Asn Val Gly Met Tyr Xaa
1 5 10

<210> 12

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<223> Synthetic

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<222> (8)..(8)

<223> xaa = Nle, which is norleucine

<220>

<221> misc_feature

<222> (10)..(10)

<223> Cys is an amide, i.e., C(=O)NH

<220>

<221> misc_feature

<222> (1)..(10)

<223> Glu at position 1 and Cys are bridged together, making this peptide cyclic

<400> 12

Glu Leu Tyr Glu Asn Val Gly Xaa Tyr Cys
1 5 10

<210> 13

<211> 10

<212> PRT

214683.ST25

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> misc_feature

<222> (8)..(8)

<223> Xaa at position 8 is Nle, which is norleucine

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa at position 10 is Adi, which is alpha-amino-adipic acid

<220>

<221> misc_feature

<222> (10)..(10)

<223> Xaa (Adi) is an amide, i.e., C(O)NH2

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<221> misc_feature

<222> (1)..(10)

<223> Glu at position 1 and Xaa (Adi) are bridged together, making this peptide cyclic

<400> 13

Glu Leu Tyr Glu Asn Val Gly Xaa Tyr Xaa
1 5 10

<210> 14

<211> 10

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<213> Artificial Sequence

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<223> synthetic

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<221> misc_feature

<222> (1)..(1)

<223> Glu at position 1 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc_feature

<222> (4)..(4)

<223> Glu at position 4 is modified to Glu(OtBu), which is tert-butoxy-glutamic acid

<220>

<221> misc_feature

<222> (5)..(5)

<223> Asn at position 5 is modified to Asn(Trt), which is trytyl-asparagine

<220>

<221> misc_feature

<222> (9)..(9)

<223> Tyr at position 9 is modified to Tyr(OtBu), which is tert-butoxy-tyrosine

<220>

<221> misc_feature

<222> (10)..(10)

<223> xaa = Adi(OAl), which is allyloxy-alpha-amino-adipic acid

<220>

<221> misc_feature

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<222> (10)..(10)

<223> Xaa is an amide, i.e., C(O)NH

<400> 14

Glu Leu Tyr Glu Asn Val Gly Met Tyr Xaa
1 5 10

<210> 15

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Synthetic

<220>

<221> misc_feature

<222> (4)..(4)

<223> Tyr at position 4 is modified to pTyr, which is phosphotyrosine

<400> 15

Lys Pro Phe Tyr Val Asn Val
1 5

<210> 16

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<223> Synthetic

<220>

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<222> (2)..(2)

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<223> Tyr at position 2 is modified to pTyr, which is phosphotyrosine

<400> 16

Phe Tyr Val Asn Val
1 5

<210> 17

<211> 5

<212> PRT

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<400> 17

Leu Tyr Glu Asn Val
1 5

<210> 18

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<223> Synthetic

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<222> (1)..(1)

<223> xaa = Gla, which is gamma-carboxy-L-glutamic acid

<400> 18

Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys Ala Ala Val Ala Leu Leu
1 5 10 15

Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
20 25

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<222> (1)..(1)
<223> xaa = Gla, which is gamma-carboxy-L-glutamic acid

<220>
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<222> (1)..(1)
<223> xaa (Gla) has a CH₂CO- group attached

<220>
<221> misc_feature
<222> (10)..(10)
<223> Cys is an amide, i.e., C(O)NH

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Xaa Leu Tyr Glu Asn Val Gly Met Tyr Cys Ala Ala Val Ala Leu Leu
1 5 10 15
Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
20 25